IN THE SPECIFICATION

Please replace the paragraph on page 7, lines 1-12 with the following replacement paragraph:

The comparison of the AChE1 according to the invention with the insect AChEs available on the databases, by alignment of the sequences corresponding to the central region as defined above, using the BLAST program (~~http://www.ncbi.nlm.nih.gov/gorf/bl2.html~~, default parameters, inactivated filter) available on the worldwide web at ncbi.nlm.nih.gov/gorf/bl2. html shows that:

- the insect AChE1 and AChE2 sequences exhibit 36-39% identity (53-57% similarity) with one another,

- the insect AChE1 sequences exhibit 65-97% identity (79-98% similarity) with one another,

- the insect AChE2 sequences exhibit 58-99% identity (73-99% similarity) with one another.

Please replace the four paragraphs beginning on page 21, line 26 and ending on line 3 of page 23 with the replacement paragraphs below:

- figure 1 illustrates the amino acid sequence alignment for the AChE1 proteins of *Anopheles gambiae, Schizaphis graminum, An. stephensi, Aedes aegypti, Drosophila melanogaster, Lucilia cuprina, Musca domestica* and *Culex pipiens*. By convention, the amino acids are numbered with reference to the AChE sequence from the torpedo fish (*Torpedo californica*; SWISSPROT P04058). The N- and C-terminal sequences are not represented due to their variability. The amino acids that are conserved between AChE1 and AChE2 are indicated in gray. The amino acids specific for AChE2 are indicated in black. The 3 residues representing the catalytic triad (S_{200}, E_{327} and H_{440}) have boxes drawn round them. The choline-binding site (W_{84}) is underlined. The circles represent the position of the 14 aromatic residues bordering the active site gorge in the *Torpedo* AChE, 10 of which are present in all the AChE1s and AChE2s (solid circles), the others not being conserved (open circles). Three intramolecular disulfide bonds between cysteine residues are indicated. The horizontal arrow indicates the position of the fragment K (amplified by means of the primers PdirAGSG and PrevAGSG). The hypervariable region of AChE2, which is absent in AChE1,

is enclosed in a box; the following sequence identifiers appear in Fig. 1: Agam1 (SEQ ID NO: 131), Sgra (SEQ ID NO: 132), Agam2 (SEQ ID NO: 133), Aste (SEQ ID NO: 134), Aaeg2 (SEQ ID NO: 135), Dmel (SEQ ID NO: 136), Lcup (SEQ ID NO: 137), Mdom (SEQ ID NO: 138), Cpip (SEQ ID NO: 139), Cpip1 (SEQ ID NO: 8) and Aeg1 (SEQ ID NO: 9).

- figure 2 illustrates the genetic detection of mosquitoes resistant to organophosphorus compounds and/or to carbamates by PCR-RFLP:

- figure 2A represents the comparison of the amino acid sequence of fragment K of various mosquito species: Cx Pip (*Culex pipiens*), Ae alb (*Aedes albopicus*), Ae aeg (*Aedes aegypti*), An alb (*Anopheles albimanus*), An gamb (*Anopheles gambiae*), An fun (*Anopheles funestus*), An nil (*Anopheles nili*), An sac (*Anopheles sacharovi*), An pse (*Anopheles pseudo-punctipennis*). The variant amino acids are shaded. The following sequences are identical: *An. darlingi* and *An. albimanus*; *An. sundaicus*, *An. gambiae* and *An. arbiensis*; *An. moucheti*, *An. funestus* and *An. minimus*; *An. stephensi* and *An. saccharovi*; the following sequence identifiers appear in Fig. 2A: Ae alb (SEQ ID NO: 10), Ae aeg (SEQ ID NO: 9), An alb (SEQ ID NO: 20), An gamb (SEQ ID NO: 140), An fun (SEQ ID NO: 16), An nil (SEQ ID NO: 21), An sac (SEQ ID NO: 18), An pse (SEQ ID NO: 17) and Cx Pip (SEQ ID NO: 8).

- figure 2B illustrates the comparison of the nucleotide sequences corresponding to fragment K of the sensitive (S-LAB) and resistant (SR) strains. The variant nucleotides are shaded (t → c at position 3; a → g at position 84: the *EcoRI* site (gaattc) located around this position, used for the PCR-RFLP analysis, is present only in the S-LAB strain; c → t at position 173). Figure 2C illustrates the restriction profiles obtained after agarose gel electrophoresis of the products of digestion with *EcoRI*, of fragment K amplified by PCR. The sensitive homozygous S-LAB strain has a profile characterized by 2 bands (214 bp and 106 bp), the resistant homozygous strain has a profile characterized by a single band of 320 bp and the resistant mosquitoes derived from the back cross have a heterozygous profile characterized by 3 bands (320 bp, 214 bp and 106 bp); the following sequence identifiers appear in Fig. 2B: Ace1-SLAB (SEQ ID NO: 24), Ace1-SR (SEQ ID NO: 25);

Please replace the paragraph beginning on page 23, line 6 with the following replacement paragraph:

- figure 3 illustrates the phylogenetic tree for the AChE proteins. The phylogenetic analysis was carried out using 47 sequences of AChE proteins from 35 different species

originating from the ESTHER database (~~http://www.ensam.inra.fr/cgi-bin/ace/index~~) (available on the worldwide web at ensam.inra.fr/cgi-bin/ace/index). The sequences were aligned and a tree was constructed as described in example 1. Only the nodes corresponding to "bootstrap" values > 50% (i.e. scores greater than 500) are indicated. The scale represents a divergence of 10%. Agam: *An. gambiae*; Aeg: *Aedes aegypti*; Aste: *Anopheles stephensi*; Cp: *Culex pipiens*; Dme1: *Drosophila melanogaster*; Lcup: *Lucilia cuprina*; Mdom: *Musca domestica*; Ldec: *Leptinotarsa decemlineata*; Ame1: *Apis mellifera*; Ncin: *Naphotettix cincticeps*; Sgra: *Schizaphis graminum*; Rapp: *Rhipicephalus appendiculatus*; Bmic: *Boophilus microplus*; Bdec: *Boophilus decoloratus*; Hsap: *Homo sapiens*; Btau: *Bos taurus*; Fcat: *Felix catus*; Ocun: *Oryctolagus cuniculus*; Rnor: *Rattus norvegicus*; Mmus: *Mus musculus*; Ggal: *Gallus gallus*; Drer: *Danio reno*; Eele: *Electrophorus electricus*; Tamr: *Torpedo marmorata*; Tcal: *Torpedo californica*; Bfas: *Bungarus fasciatus*; Mglu: *Myxine glutinosa*; Bflo: *Branchiostoma floridae*; Blan: *Branchiostoma lanceolatum*; Cint: *Ciona intestinalis*; Csav: *Ciona savignyi*; Cele: *Caenorhabditis elegans*; Cbrig: *Caenorhabditis briggsae*; Dviv: *Dictyocaulus viviparus*; Lopa: *Loligo opalescens*;

Please replace the paragraphs on page 24, lines 1-31 with the following replacement paragraphw:

- figure 5 illustrates the comparison of the amino acid sequences of the AChE1 protein of *C. pipiens*, between an insecticide-sensitive strain (S-LAB) and an insecticide-resistant strain (SR). The single mutation glycine $_{247(119)}$ → serine $_{247(119)}$ (indicated with shading) is responsible for the insecticide resistance in mosquitoes of the species *C. pipiens*; it corresponds to the substitution of the glycine located at position 247 of the sequence of *C. pipiens* AChE1 (or at position 119, with reference to the sequence of the torpedo fish AChE), with a serine; the following sequence identifiers appear in Fig. 5: SR (SEQ ID NO: 57) and S-LAB (SEQ ID NO: 7);

- figures 6A and 6B illustrate the comparison of the nucleotide sequences encoding the *C. pipiens* AChE1 protein, between an insecticide-sensitive strain (S-LAB) and an insecticide-resistant strain (SR); all the mutations are silent, with the exception of the mutation at position 739 (G → A), which results, firstly, in the substitution of the glycine codon (GGC) at position 247 of the sequence of the AChE1 protein of the sensitive strain (S-LAB) with a serine codon (AGC) responsible for insecticide resistance in the SR strain and, secondly, in the appearance of an *Alu I* site (AGCT) in the sequence of the resistant

strain, that is useful for detecting the mutation. The mutation (G → A) at position 739 of the nucleotide sequence and the mutation glycine → serine at position 247 of the amino acid sequence are indicated with shading. The sequences of the primers used for detecting the mutation at position 739 (primer Ex3dir and Ex3rev), and also the *Alu I* site are indicated in bold and are underlined; the following sequence identifiers appear in Figs. 6A and 6B: amino acid sequence 1 (on top)(SEQ ID NO: 7), S-lab (SEQ ID NO: 141), SR (SEQ ID NO: 56) and amino acid sequence 2 (on bottom) (SEQ ID NO: 57).

Please replace the paragraph beginning on page 25, line 22 with the following replacement paragraph:

- figures 9A and 9B illustrate the comparison of the sequences of the *An. gambiae ace-1* gene, between an insecticide-sensitive strain (KISUMU) and an insecticide-resistant strain (YAO); all the mutations are silent, with the exception of two mutations: the first corresponds to the replacement of the valine (CGT) at position 33 of the sequence of the AChE1 of the sensitive strain (SEQ ID NO. 5) with an alanine (CGC) in the resistant strain, and the second is the same mutation, glycine (GGC) → serine (AGC) as that found in *Culex pipiens*. The mutation glycine (GGC) → serine (AGC) results in the appearance of a second *Alu I* site (AGCT) in the sequence of the third coding exon of the resistant strain, that is useful for detecting the mutation. The coding sequences of the *ace-1* gene are indicated in bold and the mutations are indicated with shading. The sequences of the primers Ex3AGdir and Ex3Agrev used for detecting the mutation glycine (GGC) → serine (AGC), and also the *Alu I* sites of the third coding exon, are indicated in bold and are underlined; the following sequence identifiers appear in Fig. 9: amino acid sequence 1 of Kisumu (SEQ ID NO: 142), KISUMI (SEQ ID NO: 143), YAO (SEQ ID NO: 12) and amino acid sequence 2 (at bottom)(SEQ ID NO: 144);

Please replace the paragraphs beginning on page 26, line 32 and ending on line 4 of page 27 with the following replacement paragraphs:

- figure 13 represents the alignment of the nucleotide sequences of the 194 bp fragment from *Anopheles gambiae*, from *Culex pipiens* and from *Anopheles albimanus*, that are sensitive (S) or resistant (R). Light shaded background: sequences corresponding to the primers Moustdir1 and Moustrev1. Shaded background: *Alu I* site. Dark shaded background:

guanine of the Gly codon of sensitive individuals; sequence identifiers appearing in Fig. 13 are: An gam S (SEQ ID NO: 145), An gam R (SEQ ID NO: 146), C pip S (SEQ ID NO: 147), C pip R (SEQ ID NO: 148), An alb S (SEQ ID NO: 149) and An alb R (SEQ ID NO: 150);

- figure 14 represents the nucleotide sequences of the 194 bp fragment of sensitive (S) and resistant (R) *Anopheles albimanus*. The codon specifying Gly (GGC) and Ser (AGC) is in bold. The *Alu I* site is underlined. Sequence identifiers appearing in Fig. 14: An.albi."S" (SEQ ID NO: 149) and An.albi."R" SEQ ID NO: 150).

Please replace the paragraph beginning on page 31, line 24 with the following replacement paragraph:

d) Sequence analysis and gene assembly

All the sequence analyses were carried out based on the crude sequences of *Anopheles gambiae* available on the INFOBIOGEN server (~~http://www.infobiogen.fr~~) (available on the worldwide web at infobiogen.fr) and the tools available on the site (~~http://www.ncbi.nlm.nih.gov/blast/blast~~) (available on the worldwide web at ncbi.nlm.nih.gov/blast/blast). The genomic sequences encoding an AChE were identified using the TBLASTN and BLAST programs (Altschul et al., J. Biol. Mol., 1990, 215, 403-410). The genomic sequences identified were assembled using the ABI Prism Auto-Assembler program (v2.1, Perkin Elmer). The sequences were verified and corrected using the Ensembl Trace Server program (~~http://trace.ensembl.org/~~)(available at trace.ensembl.org/). Two concatenations of, respectively, 5195 and 6975 base pairs, encoding respectively AChE1 and AChE2, were assembled from, respectively, 64 and 74 independent sequences (mean redundancy of 10.5 and 6.5). The exons and the protein sequences were identified using a combination between the FGENESH (~~http://www.sanger.uk~~) (available on the worldwide web at sanger.uk) and BLASTX (~~http://www.ncbi.nlm.nih.gov~~) (available on the worldwide web at ncbi.nlm.nih.gov)programs. The genomic sequences of ascidian AChE were assembled from crude sequences deposited in the databases of the NCBI (*Ciona savignyi*) and of the Doe Joint Institute (*Ciona intestinalis*, http://www.jgi.doe.gov/programs/ciona/ciona-mainage.html). The searches in the *Drosophila* databases were carried out using Flybase (~~http://www.fruitfly.org/~~) (available on the worldwide web at fruitfly.org/).